ETS and Heart Disease

Introduction

This notebook discusses and provides copies of the public literature bearing directly on the claim that environmental tobacco smoke (ETS) is related to heart disease. Most of this literature is epidemiological, with a current total of 11 studies presenting data on a possible statistical association between ETS and heart disease incidence or mortality.

These epidemiological reports are important because they are the primary basis for claims of an elevated heart disease risk in nonsmokers exposed to ETS. However, the literature also contains claims of special harm in compromised individuals, such as heart disease patients, or regarding biochemical effects that might mediate an adverse effect of ETS on heart disease incidence or mortality. Accordingly, this notebook also includes several laboratory and statistical reports dealing with ETS and exercise performance, particularly in angina patients, or with biochemical factors suggested as involved in the development of heart disease.

Each of the articles included in this notebook has been highlighted in blue and yellow. The blue highlighting identifies the most notable comments supporting a relationship of ETS with heart disease, or that are otherwise adverse regarding tobacco or smoking. The yellow highlighting identifies comments that

challenge, or at least that are concessionary concerning, the potential involvement of ETS or tobacco in disease causation.

The initial section of this notebook contains an overview and discussion of the literature. The literature itself is grouped into four appendices. Appendix A (Tabs 1-13) contains the primary epidemiological reports, consisting of 11 studies reported in 13 articles. A summary and discussion of major criticisms is provided for each individual study. Appendix B (Tabs 14-17) contains the major meta-analyses and reviews concluding that ETS is associated with an elevated heart disease risk. Appendix C (Tabs 18-23) contains the primary reviews which have judged that the data are inadequate to conclude that ETS is related to heart disease. Appendix D (Tabs 24-35) contains a mixed group of articles which provide data concerning ETS in relation to exercise performance, potential effects in heart patients or in relation to cardiovascular biochemical and cellular processes. Short summaries are provided with the articles in Appendix D. If notable letters to the editor or other editorial comments were published concerning any of the articles in this notebook, these materials were also included.

Epidemiologic Reports and Reviews

Reports with original data

There are currently 11 studies (in 13 reports) presenting epidemiological data on a possible statistical association between ETS and heart disease incidence and mortality. There are 13 reports, because for two studies, the data were presented in two separate articles. It should be emphasized, however, that the epidemiological reports on the heart disease issue include several scientifically weak sources, particularly meeting abstracts. Furthermore, all of these studies are open to serious methodological criticisms. Summaries of the individual studies, as well as a list of the major criticisms of each, are provided with the highlighted copies of the articles in Appendix A.

The ETS associated risks reported in the 11 epidemiological studies are summarized in the following table.

ETS/Heart Disease Epidemiological Reports

	Sex	Reported Risk	Statistical Testing
Butler (1990)[1]	F	RR = 1.40	0.51 - 3.84 (95% CI)
Garland et al. (1985)[2]	F	RR = 2.7	$p \leq .10$
		Ctrl vs. ETS	
Gillis et al. (1984)[3]	M	31 vs 45 per 10^4/yr	No stat. test rpted.
	F	4 vs 12 per 10^4/yr	No stat. test rpted.
*He, et al. (1989)[4]	F	OR = 1.50	$p < .01$
*Helsing, et al. (1988)[5]	M	RR = 1.31	1.1-1.6 (95% CI)
	F	RR = 1.24	1.1-1.4 (95% CI)
Hirayama (1984)[6]	F	RR = 1.31 (husbands smoking $\geq$ 20 cigs/day)	1.06-1.63 (90% CI)
*Hole, et al. (1989)[7]	M+F	RR = 2.01	1.21-3.35 (95% CI)
Humble, et al. (1990)[8]	F	RR = 1.59	0.99-2.57 (95% CI)
Lee, et al. (1986)[9]	M+F	RR = 1.03	0.65-1.62 (95% CI)
*Martin, et al. (1986)[10]	F	RR = 3.4	$p < .01$
Palmer, et al. (1988)[11]	F	RR = 1.2	No stat. test rpted.
*Sandler, et al.(1989)[12]	M	RR = 1.31	1.05-1.64 (95% CI)
	F	RR = 1.19	1.04-1.36 (95% CI)
Svendsen, et al. (1987)[13]	M	RR = 2.23	0.72-6.92 (95% CI)

NOTE: Gillis, et al. (1984) and Hole, et al. (1989) are based on the same study. Also, Helsing, et al. (1988) and Sandler, et al. (1989) are based on the same study.

*Reported to be statistically significant at the 95% level of confidence.

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In an overall evaluation of the epidemiological reports, it is important to consider the issue of statistical significance. Some fluctuation in disease or mortality rates will occur simply by chance alone. Hence, when these rates are compared, as in risk ratios, it is necessary to apply a standard to determine the statistical likelihood that an apparent elevation or reduction in risk reflects chance variation or whether it reflects an actual difference in the comparison groups. The traditional scientific standard is to require that a statistical test indicate at least a 95% probability that an observed difference reflects a true effect. Stated in reverse, this would mean that the standard only allows a 5% probability that the result was due to chance.

When discussing relative risks, if the disease or mortality rates are equivalent in the comparison groups, this will be reflected in a ratio of 1.0. When a statistical test is performed, the 95% standard is met when the 95% confidence intervals are reported not to include 1.0. Sometimes a "p" value is given, which states the probability that an observation is due to chance. Hence, a statement of "p < .05" means that the observation could have occurred by chance less than 5% of the time. To state "p < .05" or to provide 95% confidence intervals that do not include 1.0, are equivalent indications of statistical significance.

Only four of the 11 epidemiological studies regarding ETS and heart disease report a statistically significant result at the 95% level of confidence. (1) He, et al. (1989), a Chinese language report based on only 34 female heart disease patients; (2) Helsing, et al. (1988)/Sandler, et al. (1989), a study based on a Maryland census in which the information regarding spousal smoking (used to estimate ETS exposure) was from 1963; (3) Hole, et al. (1989), a Scottish study based on only 84 heart disease deaths; and (4) Martin, et al. (1988), a report based on 23 women who reported having a heart attack and which was given a conference but apparently not otherwise accepted for publication.

In sum, seven of the 11 studies of ETS exposure and heart disease have failed to report a statistically significant association. In the four studies that have claimed a statistically significant relationship, two were from outside the United States. Three were very small-scale. All of these studies suffer from a variety of serious methodological weaknesses.

A list of the most common weaknesses in the individual studies is provided below. It will be recognized that these are characteristic of epidemiological studies of ETS in general, not simply those relating to heart disease. For a more detailed discussion of the criticisms applicable to each study, see Appendix A.

1. Small sample sizes.

2. Lack of statistical significance, or failure to test for statistical significance.

3. Potential misclassification of the smoking status of study participants.

4. Inadequate assessment of ETS exposure.

5. Failure to control adequately for biases stemming from potential confounding variables.

6. Failure to confirm causes of death via autopsy or other histological methods.

Reviews claiming ETS-associated risk

Despite the scientific weaknesses in the epidemiologic literature on ETS and heart disease, four recent reviews have concluded that ETS is associated with an increased risk of heart disease and that, in fact, such exposure causes a large number of deaths each year. Copies of these reviews are provided in Appendix B. Each of these reviews attempted to estimate an overall risk based on the combined data from the epidemiologic studies. These estimated risk ratios and the associated 95% confidence intervals are provided in the following table.

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Meta-Analyses and Reviews of ETS-Heart Disease Data

		RR	95% CI
Wells (1988)[14]	Males	1.31	(1.1-1.6)
	Females	1.23	(1.11-1.36)
	Home		
Kawachi, et al. (1989)[15]	Males	1.3	(1.1-1.6)
	Females	1.2	(1.1-1.4)
	Workplace		
	Males	2.3	(1.4-3.4)
	Females	1.9	(1.4-2.5)
Kristensen (1989)[16]	Both sexes	≈ 1.3	
Glantz and Parmley (1991)[17]	Both sexes	1.3	(1.2-1.4)

These estimates were generally derived from the statistical technique known as meta-analysis. (The Kristensen article appears to be an exception, in that the estimated 1.3 relative risk was apparently based on an informal estimation and no confidence intervals were given.) Although these reviews varied somewhat in form, detail and focus, the estimates were generally similar, about 1.3, reflecting a 30% elevation in risk associated with ETS exposure.

The Kawachi, et al. (1989) discussion was fairly narrowly focused on New Zealand. The Kristensen (1989) discussion was a

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limited part of a larger discussion of factors involved in cardiovascular diseases and the work environment. Thus, the major reviews, both of which clearly involved meta-analytic techniques, were those by Wells in 1988 and by Glantz and Parmley in 1991. These two reports are discussed further below.

A. Judson Wells, a consultant to the American Lung Association, statistically combined the data from several reports on ETS and heart disease, including both prospective (cohort) and case-control studies. He then calculated overall relative risks (ETS exposed versus nonexposed) for lung cancer (1.44 for females; 2.1 for males), cancers other than lung (1.16 for females; no risk elevation for males) and heart disease (1.23 for females; 1.31 for males). He also estimated numbers of death related to these disease categories, claiming that ETS exposure results in 46,000 deaths per year in nonsmokers. Of these, 3,000 are claimed to be from lung cancer. For cancers other than the lung, he calculated that ETS exposure results in 11,000 annual deaths. The largest number of deaths from ETS exposure was claimed to be due to heart disease. He claimed that 32,000 nonsmoker heart disease deaths per year stem from ETS exposure.

The most recent, and certainly the most widely publicized, review of ETS and heart disease was undertaken by two authors from the Department of Medicine, University of California, San Francisco.

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In their 1991 paper, Stanton Glantz and William Parmley conclude that ETS exposure is statistically associated with an estimated 30% increase (relative risk of 1.3) in heart disease risk in nonsmokers. They argue that this translates into 37,000 heart disease deaths in nonsmokers stemming from ETS exposure. Glantz and Parmley also discuss a number of biochemical and experimental studies which purportedly support the biological plausibility of such a relationship.

In evaluating the claims by Wells and by Glantz and Parmley, it should be emphasized that meta-analysis, the technique from which they derive their risk estimates, is appropriately used only when the underlying studies are highly similar and of high quality. If the underlying studies are based on different populations and procedures and suffer from serious methodological weaknesses, then any meta-analysis will consequently be invalidated.

The above considerations are directly applicable to an evaluation of the risk claims regarding ETS and heart disease. These claims are based on meta-analyses of a small group of epidemiological studies reporting a relationship between ETS exposure and an increased risk of heart disease. In general, these studies deal with spousal smoking and assess heart disease risk in the nonsmoking spouse. Otherwise, these studies used widely disparate methodologies, study populations and endpoints. Several

are very weak, preliminary, available only in abstract form, or are based on such scanty data that they quite arguably are not sufficiently reliable or valid even to be considered seriously in a meta-analysis. Appendix A contains discussions of the major flaws in the individual studies.

Reviews emphazing inconclusiveness of the data

Reviews such as those by Wells and by Glantz and Parmley often receive a great deal of publicity. However, it is important to recognize that there have been a number of other examinations of the data concerning ETS and heart disease. Several important reviews have concluded that the data on this issue are equivocal and inadequate to support claims of an increased heart disease risk in nonsmokers exposed to ETS.

The first major reviews of the epidemiological data on ETS and heart disease appeared in 1986. In that year, a report of the United States Surgeon General[18] examined the available data and judged that "no firm conclusion" (p. 10) could be made regarding a possible relationship between ETS and heart disease. Also in 1986, a similar evaluation appeared from a committee of the National Research Council of the National Academy of Sciences.[19] This committee calculated that any potential heart disease risk related to ETS would be "difficult to detect or estimate reliably" from

epidemiological studies, and would be "the same order of magnitude as what might arise from expected residual confounding due to unmeasured covariates." (p. 263)

Thus, both the 1986 Surgeon General's Report and the National Research Council report judged that the data were insufficient to allow a conclusion that ETS exposure is a cause of heart disease. Even the 1991 review by Glantz and Parmley recognized this as a "reasonable" position, at least in 1986. On the other hand, Glantz and Parmley argued that data published since 1986 warrant that this conclusion be modified. However, other scientists have undertaken more balanced and critical reviews of the more recent data and have judged that it remains inconclusive. The four most significant of these reviews, and their conclusions, are as follows:

a. At a major conference on ETS held at McGill University in 1989, Lawrence Wexler, of the New York Medical College, concluded that recent data did not provide a basis for altering the earlier conclusions by the Surgeon General and National Research Council concerning ETS and cardiovascular disease.

> Based on the available evidence, it is this author's opinion that it has not been demonstrated that exposure to ETS increases the risk of cardiovascular disease. (p. 139)[20]

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b. A similar evaluation was made by two scientists from the United Kingdom, who reviewed the literature on ETS and heart disease and presented their conclusions at an international conference on indoor air quality held in Lisbon, Portugal in April 1990.

> It is concluded that no increased risk of cardiovascular disease can be associated unequivocally with exposure to ETS, and it seems probable that this will continue to be the case until specifically designed trials are instigated, and some objective measure of degree of exposure can be devised. (p. 215)[21]

c. Another scientific review of this literature was performed by two physicians from the University of Munich, Germany and given at an international conference in Hungary in June 1990. The conclusion was similar.

> Taking into account the small increase in coronary risk in passive smokers as compared to non-exposed subjects and also the low validity and small number of epidemiological studies available and the fact that their results are at least inconsistent, a relationship between passive smoking and cardiovascular diseases cannot be established on these data. (p. 6)[22]

d. In a 1991 book discussing a wide range of issues involving ETS, the literature on heart disease was reviewed by Alan Armitage, former director of toxicology of a major European research laboratory and now head of pharmacology at

the Tobacco Research Council Laboratories in the United Kingdom. He judged that the scientific data have not established an increased heart disease risk in nonsmokers exposed to ETS.

> It is clear that the evidence for a harmful effect of ETS in enhancing CHD [coronary heart disease] risk in non-smokers is not very convincing. . . . (p. 114)[23]

Studies Involving Exercise Performance, Heart Disease Patients and Biochemical Measurements

There are several experimental and biochemical studies that have been cited in the literature as supporting an increase in heart disease risk stemming from ETS exposure. A few of these reports claim that ETS exposure adversely effects exercise capacity and that in the case of heart disease patients, this can lead to attacks of angina (heart pain). Other reports have attempted to demonstrate that ETS exposure adversely affects some aspect of cardiovascular function, such as blood clotting (platelets), myocardial respiration (oxygen usage) or cholestol levels. These articles, with brief summaries, are provided in Appendix D.

In an overall evaluation of these studies, it is important to note that they constitute a relatively minor aspect of the ETS/heart disease issue. That is, the claim that ETS increases the risk of heart disease is a statistical statement based on epidemiological reports. Once having made that statement, various

kinds of studies dealing with cardiovascular or exercise performance or with mechanisms might be marshalled to argue for its plausibility. On the other hand, without the epidemiological underpinning, such studies would probably be much less notable since there would be nothing that they would be attempting to explain.

In the area of exercise performance, there are three primary studies. In one of these, a 1985 report by McMurray, et al.,[24] healthy subjects were used and ETS exposure was claimed to have an adverse effect on exercise performance. Two other studies, one by Aronow (1978)[25] and the other by Khalfen and Klochkov (1987)[26] used angina patients. In somewhat similar study designs, both reports claimed that when these heart disease patients were exposed to ETS, they were not able to exercise as long before experiencing angina. The credibility of the Aronow report has been widely challenged in the literature. The Khalfen and Klochkov report is a Russian language article about which relatively little is known. Regarding any of the exercise performance studies, whether with healthy or heart disease patients, a general criticism is that when dealing with ETS, it is almost impossible to "blind" either the experimenter or the subjects with regard to ETS exposure. Thus, the possibility is always open that some subjective factor may influence the results.

There are very limited data attempting to demonstrate that ETS adversely affects some process that might be involved in blood clotting (thrombus formation) or atherosclerosis. The primary focus has been on the possibility that ETS may increase the tendency of certain blood components, known as platelets, to stick together. This claim has been made based mainly on data in four published reports. Three of these are from the same Austrian research group. (Sinzinger and Kefalides, 1982[27]; Burghuber, et al., 1986[28]; Sinzinger and Virgolini, 1989[29]) Of these three, one is merely a letter to the editor (Sinzinger and Kefalides, 1982) and another is a German language article with only an English abstract (Sinzinger and Virgolini, 1989). The fourth report, Davis, et al., (1989)[30] is from a group of researchers in Kansas City, Missouri. It suffers from serious methodological weaknesses, particularly its failure to establish a proper control condition.

Finally, there are two reports of children which assessed cholesterol and other blood components in relation to parental smoking status (Moskowitz, et al., 1990[31]; Pomrehn, et al., 1990[32]), one of which (Pomrehn, et al., 1990) is only available as an abstract from a meeting presentation. Both reports claimed that parental smoking was associated with decreases in HDL cholesterol, which some literature has argued may be associated with heart disease risk. These studies measured components of blood as the endpoint, but are essentially epidemiological studies in that they,

at best, may suggest statistical correlations. As such, they suffer from weaknesses characteristic of other epidemiological studies of ETS exposure, especially difficulties in controlling for potential confounding variables and inadequate assessment of ETS exposure. Furthermore, the potential significance of blood values in relation to later heart disease risk in a group of children is highly speculative.

This notebook also contains a group of three articles relating to research from a Czechoslovakian group, which claims that "passive smoking" has an adverse effect on the heart's use of oxygen.[33] [34] [35] These were animal studies involving smoke exposure to rabbits. They clearly involved a design intended to mimic "active" smoking, and are included in this notebook merely because they were erroneously discussed in the 1991 Glantz and Parmley paper as providing data relevant to ETS exposure.

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Endnotes

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